2009, *4(1)*. [2] C. Abad-Zapatero, O. Perišić, J. Wass, A.P. Bento, J. Overington, B. Al-Lazikani, M.E. Johnson, *Drug Discovery Today,* ***2010***, *15 (19-20)*, 804–811. [3] A.L. Hopkins, C.R. Groom, A. Alex, *Drug Discovery Today,* ***2004***, *9*, 430-431. [4] C. Abad-Zapatero, J. T. Metz. *Drug Discovery Today*, ***2005***, *10 (7)*, 464-469. [5] D. Blasi, G. Arsequell, G. Valencia, J. Nieto, A. Planas, M. Pinto, N.B. Centeno, C. Abad-Zapatero, J. Quintana, *Molecular Informatics*, ***2011***, *30*, 161-167.

Keywords: transthyretin, amyloid, chemico-biological space.

MS16.P06

Acta Cryst. (2011) A**67,** C288

Structural basis for inhibition of interferon alpha signaling pathway and its therapeutic potential in SLE patients

Zhi-Jie Liu[a], Songying Ouyang,[a] Bin Gong,[b] Jin-Zhi Li,[c] Li-Xia Zhao,[a] Guo-Ping Zhao,[d] Ying Wang,[c,d] Mi-Fang Liang,[b] [a]*National Laboratory of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China.* [b]*State Key Laboratory for Infectious Disease Control and Prevention, National Institute for Viral Diseases Control and Prevention, China CDC.* [c]*Shanghai Institute of Immunology, Institute of Medical Science, Shanghai Jiaotong University School of Medicine, Shanghai, China.* [d]*Shanghai-MOST Key Laboratory for Health and Disease Genomics, Chinese National Human Genome Center at Shanghai, Shanghai, China.* E-mail: zjliu@ibp.ac.cn

Increasing evidences suggest that the type I interferon (IFN) plays a critical role in the etiopathogenesis of systemic lupus erythematosus (SLE), which makes it a promising therapeutic target for the treatment of the disease. By screening a large size non-immune human antibody library, we have developed a human single-chain antibody (ScFv) AIFNα1bScFv01 and corresponding whole antibody AIFNα1bIgG01, that recognizes recombinant human interferon alpha1b (hIFNα1b) with high specificity and high affinity. The IgG antibody can down-regulate the expression of *ISG15* and *IFIT-1* induced by either recombinant hIFNα1b or naive IFN-α presented in SLE patient's sera. The crystal structure of AIFNα1bScFv01-hIFNα1b complex solved to 2.8 Å resolution reveals that both Pro26-Gln40 region in loop AB and Glu147-Arg150 region in helice E of hIFNα1b contribute to binding with AIFNα1bScFv01. Four residues of above two regions (Leu30, Asp32, Asp35 and Arg150) are critical for the formation of antigen-antibody complexes. AIFNα1bScFv01 shares partial epitopes of IFNα1b with its receptor IFNAR2. AIFNα1bIgG01 has a much higher affinity for IFNα1b than IFNAR2 (K_D = 0.747 nM versus 100 nM), making it unavailable for binding to IFNAR2 and preventing the activation of IFN-α-mediated signaling pathway. Thus, AIFNα1bIgG01 exhibits its neutralizing activity through competition with IFNRA2 to bind with IFN-α. Our results highlight the potential use of the human antibody for modulating the activity of IFN-α in SLE.

Keywords: SLE, IFNα, ScFv antibody

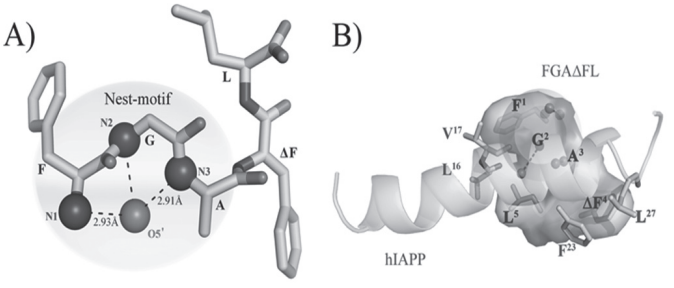
MS16.P07

Acta Cryst. (2011) A**67,** C288

Structure of peptide inhibitor of human islet amyloid polypeptide fibrillization

Anurag Misra,[a] Aseem Mishra,[b] Vaishnavi Murthy,[b] Madhavi Gupta,[b] Bhaskar Bhushan,[b] Suryanarayanarao Ramakumar,[a] Virander Singh Chauhan[b] [a]*Department of Physics, Indian Institute of Science, Bangalore-560012, India*. [b]*International Centre for Genetic Engineering and Biotechnology, New Delhi-110067, India*. E-mail: anurag@physics.iisc.ernet.in

Type-2 diabetes mellitus (T2DM) accounts for more than 90% of all diabetes worldwide. Over 100 million people worldwide have T2DM, and the prevalence is increasing dramatically in both the developed and developing countries. Amyloid deposits have been observed in a vast majority of the T2DM patients and these are primarily on account of misfolding and aggregation into fibrils of human islet amyloid polypeptide (hIAPP), a 37 residue endocrine hormone secreted by pancreatic *β*-cells. It has been suggested that intermediates produced in the process of fibrillization are cytotoxic to insulin producing *β*-cells. Hence, the inhibition of misfolding/fibrillization of hIAPP could be a possible strategy to mitigate T2DM. The misfolding of hIAPP involves structural transition from its native state (coil and/or helical and/or transient helical conformation) to *β*-sheet conformation. We have targeted hIAPP fibrillization by designing short peptides containing the helix inducing *α,β*-dehydrophenylalanine (ΔPhe or ΔF) amino acid and the fibrillization inhibition was monitored by thioflavin-T assay and electron microscopy. We find that the short peptides inhibit fibrillization without any cytotoxic effect as tested on RIN4fm pancreatic cell line. Of these, the penta-peptide, FGAΔFL is the most effective inhibitor of hIAPP fibrillization. We successfully crystallized the penta-peptide and solved its 3D structure at atomic resolution using direct methods. Molecular conformation of the peptide reveals the occurrence of a nest-motif (Fig. A) involving the stretch FGA in the penta-peptide and a type-I *β*-turn. To gain structural understanding and visualize the probable interactions of the hIAPP with FGAΔFL, molecular docking studies were performed using AutoDock4. Here, we considered the penta-peptide as receptor and $hIAPP_{6-30}$ (PDB: 2KB8) as ligand. The best ligand pose was selected from the cluster with the highest occurrence and the lowest binding energy (-6.41 kcal/mol). The interactions stabilizing FGAΔFL-hIAPP complex, are nest-motif interactions, hydrophobic interactions and aromatic interactions (Fig. B). We propose, on the basis of FGAΔFL crystal structure and molecular docking, that the penta-peptide binds to the helical conformation of hIAPP which is considered as transient in nature and/or preferred in membranous environment. Here, the penta-peptide binds at the C-terminal of helical $hIAPP_{6-30}$, stabilizes the helical conformation and makes the transition from alpha to beta structure unfavourable, thereby curtailing the fibrillization process. Thus, the crystal structure of the penta-peptide inhibitor together with computational docking studies provides an atomic level picture of the possible mechanism by which the penta-peptide manifests its fibrillization inhibition activity. Further studies are underway in our laboratories to develop even more potent inhibitors of hIAPP fibrillization and the details will be presented.



Keywords: diabetes, amyloid, inhibitor

MS16.P08

Acta Cryst. (2011) A**67,** C288-C289

Studies of nucleotide metabolism from blood fluke *Schistosoma mansoni*

Humberto M. Pereira, Ricardo DeMarco, Larissa Romanelo, Juliana R. Torini de Souza, Victor E. A. Caldas, Vitor H. B. Serrão, Alexandre